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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/660,862	09/13/2000	William Pollack	ATOPH:52516	7947

20350 7590 10/29/2003

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EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	24

DATE MAILED: 10/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/660,862	POLLACK, WILLIAM	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

1. This Office Action is responsive to Applicant's response filed June 16, 2003. Claims 10-13 have been cancelled.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Rejection Maintained

3. The rejection of claims 1 and 5-9 under 35 U.S.C. 103(a) as unpatentable over Laursen et al in view of Flaa et al is maintained for the reasons set forth on pages 3-5, paragraph 4 of the previous Office Action.

The rejection was on the grounds that Laursen et al teach a method of producing immunoglobulins and other immunoglobulin products (see the Title). Laursen et al teach a method of producing IgG4 (see Example 2, columns 17-18 and column 20, lines 9-15). Laursen et al teach the use of DEAE Sepharose® and CM-Sepharose® exchange resins in the method of producing immunoglobulin and immunoglobulin products (column 7). Laursen et al teach a method of producing immunoglobulins by starting with normal human plasma or plasma from donor with high titers of specific antibodies (i.e. hyperimmune plasma) (column 4). Laursen et al teach that the method for producing IgG immunoglobulins and immunoglobulin products include: 1) purification of the Cohn fraction by preparing Cohn fraction from human plasma by adjusting the pH, ethanol concentration, adjusting temperature and protein concentration, 2) extraction of the immunoglobulin from the Cohn extraction by adding sodium phosphate, adjusting pH, filtering, centrifuging and re-filtering the suspension and 3) purification of by serial anion and cation exchange chromatography using DEAE Sepharose® and CM-Sepharose® resins. Laursen et al teach that the IgG is eluted with a gradient of NaCl when the CM-Sepharose column is used (column 15-16). Laursen et al teach the addition of saccharides to the IgG fraction to stabilize and adjust the osmolality of the IgG fraction (column 9, lines 17-26 and column 4, lines 20-23). Laursen et al teach an osmolality of 347-350 mOsm/kg (column 23) and a pH range of 4.0-6.0 for the IgG immunoglobulin fraction (column 5, lines 12-14). Laursen et al teach that the products obtained from the invention can be freeze-dried (column 12, lines 35-37). The recitation

of "conductivity of between 3.5 to 6 millisiemens" would be an obvious experimental design choice. It is well known in the art to freeze and later thaw purified fractions at certain convenient points in the process of antibody purification. This is done to pool large amounts of purified antibody fractions before use or further processing or to store purified antibody fractions to be used at a later date. This is evidenced by Rhodes *(U.S. Patent No. 5,346, 687, published September 13, 1994),* which teaches that frozen purified antibody can be frozen in a vial and maintained for indefinite period before use (claim 5).

Laursen et al do not teach the use of lactose.

Flaa et al teach stabilizing solutions for proteins and peptides (see the Title). Flaa et al teach that bulking agents such as lactose can be added to protein compositions, if the protein compositions are going to lyophilized or frozen (column 5, lines 63-67 and column 6, lines 1-3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the lactose as taught by Flaa et al to the IgG4 composition of Laursen et al because Laursen et al teach that saccharides are added to stabilize the IgG fraction and to adjust the osmolality of the IgG fraction (column 9, lines 17-26 and column 4, lines 20-23). It would be expected barring evidence to the contrary that the method of producing IgG4 as taught by Laursen et al and Flaa et al combined would produce purified amounts of IgG4 because Laursen et al teach that purified amounts of IgG4 ranging from 0.6% to 1.5% are produced by the method (columns 17-18).

Applicant urges that Laursen et al teach a method of total IgG immunoglobulins that have not been fractionated into subtypes using anion and cation exchange resins. Applicant urges that Flaa et al teach stabilizing proteins which in some embodiments include sugars, such as lactose as bulking agents. Applicant urges that the claimed invention differs from that of the prior art because the claimed invention teaches a method of manufacturing IgG4 immunoglobulin subtype free of IgG1, IgG2 and IgG3 subtypes for the treatment of diseases and conditions including serious insect sting allergies. Applicant urges that the pure preparations prepared from the methods of the claimed invention contain less protein and more blocking antibody per unit weight, thereby conferring immunity in patients while reducing the risks of aggregation and

fragmentation of the immunoglobulin. Applicant urges that the Office fails to establish a *prima facie* case of obviousness. Applicant urges that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success and 3) the cited references do not teach or suggest all claim limitations. Applicant urges that the IgG subtypes are not separated in the teachings of Laursen et al and the method disclosed within teaches a method of producing total IgG. Applicant urges that Flaa et al does not teach or suggest any methods for purifying proteins, including immunoglobulins. Applicant urges that Rhodes et al teach only methods of radiolabeling antibodies and storage of frozen antibodies. Applicant urges that Rhodes et al do not teach conventional chromatography techniques to purify IgG4 immunoglobulins. Applicant urges that because the art of fractionation and ion chromatography is unpredictable one skilled in the art would not expect a purification system for the extraction of pure IgG from crude plasma to be relevant for the purification of an IgG4 subtype from IgG. Applicant urges that Laursen et al do not imply or otherwise provide motivation to modify the references or a reasonable expectation of success in doing so. Applicant further urges that neither Flaa et al or Rhodes et al provide motivation to modify the references to arrive at the claimed invention or a reasonable expectation of success in doing so.

Applicant's arguments filed June 16, 2003 have been fully considered but they are not persuasive. It is the Examiner's position that Applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The claims are directed to a method of manufacturing IgG4 immunoglobulin. Laursen et al teach a method of producing of IgG as well as IgG4 (see Example 2, columns 17-18 and column 20, lines 9-15). Laursen et al do not teach the use of lactose. However, Flaa et al teach stabilizing solutions for proteins and peptides (see the Title). Flaa et al teach that bulking agents such as lactose (i.e. saccharides) can be added to protein compositions, if the protein compositions are going to lyophilized or frozen (column 5, lines 63-67 and column 6, lines 1-3). It would have been obvious to add the lactose as taught by Flaa et al to the to the IgG4 composition of Laursen et al because Laursen et al teach that saccharides are added to stabilize the IgG fraction and to adjust the osmolality of the IgG fraction (column 9, lines 17-26 and column 4, lines 20-23). In response to applicant's argument regarding Rhodes et al, this reference is cited to show that it is well known in the art to freeze and later thaw purified fractions at certain convenient points in the process of antibody purification.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the claimed invention differs from that of the prior art because the claimed invention teaches a method of manufacturing IgG4 immunoglobulin subtype free of IgG1, IgG2 and IgG3 subtypes for the treatment of diseases and conditions including serious insect sting allergies and the pure preparations prepared from the methods of the claimed invention contain less protein and more blocking antibody per unit weight, thereby conferring immunity in patients while reducing the risks of aggregation and fragmentation of the immunoglobulin) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that no *prima facie* case has been established, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, there is clear motivation to add lactose (a saccharide) to the IgG4 composition to stabilize the composition and adjust the osmolality of the IgG fraction. One of skill in the art would expect that the addition of a saccharide (i.e. lactose) would be successful at stabilizing

the immunoglobulin composition. There is nothing on the record to show that the combination of teachings would not suggest the claimed invention. Therefore, the teachings of Laursen et al combined with the teachings of Flaa et al suggest the claimed invention.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
October 21, 2003

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